

Knock-in Mouse

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The present invention relates to transgenic animals, particularly to a knock-in mouse and a targeting vector intended for the generation of such an animal like a knock-in mouse. Furthermore, the present invention relates to stem cells, preferably murine embryonic stem cells comprising said targeting vector as well as to a screening method for the identification of compounds for the treatment of human epilepsy syndrome, particularly familial nocturnal frontal lobe epilepsy (ADNFLE).

10 According to recent estimations, about 0.4 to 1% of the population suffer from epilepsy, rendering it the second most frequent neurological disease. Though the available antiepileptic drugs are considered effective, sufficient seizure control is impossible with 15 to 20 % of the patients; therefore a significant risk of permanent cerebral damages is given. About every 10th heavy *status epilepticus*, i.e. heavy seizures in rapid sequence, still leads to death today.
15 40 % of the diseases pertain to idiopathic epilepsies (IE), i.e. epilepsies which no specific causes could be found for yet and which, with a prevalence of 0.6 %, pertain to the most frequent neurological diseases (Sander, 1996). Concordance rates of 80 % with identical twins and 20 % with binovular twins verify a predominantly genetic etiology. A 5-10 % risk of falling ill with first grade relatives and intra-familial variability of the IE in childhood and adolescent years indicate an involvement of several genetic factors.
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Characteristic for idiopathic autosomal dominant inherited nocturnal frontal lobe epilepsy (ADNFLE), which was only recently described (Scheffer et al., 1994, 1995), are clusters of motor seizures occurring in the non-REM phase of sleep, which usually occur for the first
25 time in the first or second decade of life. The affected patients wake up shortly after falling asleep or very early in the morning displaying non-specific aura phenomena rapidly followed by motor seizures with tonic or hyperkinetic activities. The beginning of a seizure is marked by gasps, grunts or short vocalizations. In most cases consciousness is maintained during the seizures, for which reason they are often misinterpreted as parasomniae, nightmares or hysterical seizures (Scheffer et al. 1994). ADNFLE shows a 70 % penetrance and a considerable
30 intra-familial variation of seriousness (Scheffer et al., 1997). The majority of the affected patients show a normal intellect, a normal EEG diagnosis and no neurological abnormalities (Niedermeyer, 1997, Niedemeyer, 1997b, Scheffer et al., 1995). However, in some families

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